REMARKS

I. The Amendments

The Claims have been amended for the purpose of more clearly defining what Applicants regard as the invention. Claim 14 has been canceled without prejudice. Claims 15-43 have been amended to correct an error in their numbering. Renumbered Claims 16, 19, 28, 29 and 41 also have been canceled without prejudice. Claims 4, 5, 17, 18, 20-27, 30, 35-40, 42 and 43 have been amended correspondingly to correct their dependencies. Claims 20-22 have been amended further to remove redundancies and to more clearly recite the claimed subject matter without adding new matter. Claims 15 and 23 have been amended further to clarify that the conjugate comprises an active substance selected from the group consisting of a chemotherapeutic agent and a photoactive compound. This amendment is supported in the Specification at, for example, page 2, lines 11-25. Claims 17 and 23 have been amended to correspond to amended Claim 15.

Applicants reserve the right to prosecute canceled or amendatory subject matter in one or more timely filed divisional, continuation or continuation-in-part applications. The amendments and new claims do not raise new issues and are fully supported by the Specification of the present application. Entry of the amended and new claims under 37 C.F.R. §1.111 is respectfully requested.

Instructions for amending the claims are attached hereto as *Appendix A*.

II. The Rejections

A. Rejection of Claim 14 under 35 U.S.C. § 101

Claim 14 is rejected under 35 U.S.C. § 101 for allegedly improperly defining a process. Without agreeing with the propriety of this rejection, Applicants have canceled Claim 14, thus rendering this rejection moot. Accordingly, Applicants respectfully request that this rejection be withdrawn.

B. Rejection of Claims 14, 20, 21, 22, 30, 37 and 43 under 35 U.S.C. § 112

Claims 14, 20, 21, 22, 30 and 37 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and

distinctly claim the subject matter which Applicants regard as their invention. The rejection is moot with respect to canceled Claim 14 and respectfully traversed with respect to the remaining rejected claims.

Claim 20 is rejected under 35 U.S.C. § 112, second paragraph as indefinite for redundantly reciting the presence of an azo group and for allegedly presenting an unclear description of the components of the claimed conjugates. Without agreeing with the propriety of this rejection, Applicants have amended Claim 20 to remove the objected-to language. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

Claims 21 and 22 also are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for redundantly reciting the presence of an azo group. Without agreeing with the propriety of this rejection, Applicants have amended Claims 21 and 22 to remove the objected-to language. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claim 30 is rejected as indefinite under 35 U.S.C. § 112, second paragraph for allegedly broadening the scope of Claim 23, from which it depends, by reciting that the binding comprises the formation of an ester. Applicants respectfully traverse. Claim 23 recites in relevant part a "process for the preparation of the conjugate according to Claim 15, *comprising* binding an active substance ... to a native human serum albumin ... by means of a linker *containing* an azo group" (emphases added). Claim 30 recites "[t]he process of Claim 23, wherein said binding comprises the *formation* of an ester" (emphasis added). The process of Claim 23 does not necessarily exclude the formation of an ester during the binding process. Thus, Claim 30 does not impermissibly broaden the scope of the Claim 23. Consequently, Claim 30 is not indefinite. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

Claim 37 is rejected under 35 U.S.C. § 112, second paragraph as indefinite for allegedly reciting active substances that appear from the Specification to be part of the linker structure. Applicants respectfully disagree. Each of the active substances recited in Claim 37 is described as an active substance in the Specification at, for

example, page 2, lines 18-20. Thus, Claim 37 is not indefinite. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

Claim 43 is rejected under 35 U.S.C. § 112, second paragraph as indefinite for reciting the phrase "a derivative of phenylene," which is allegedly inadequately described in the Specification. Applicants respectfully traverse.

The rejection asserts that "[a] derivative *may be* interpreted as reading on one atom derived from a phenylene" (emphasis added). Applicants respectfully point out that this is an incorrect standard of claim interpretation. During examination, a claim must be given the broadest *reasonable* interpretation that is consistent with the interpretation that those skilled in the art would reach. *See In re Cortright*, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999); *In re Morris*, 44 USPQ2d 1023, 1027-28. Consistent with this, terms must be given their "plain meaning," unless otherwise defined in the Specification. *See In re Zletz*, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). The "plain meaning" is the meaning given to a term by one of ordinary skill in the art. *See In re Sneed*, 218 USPQ 385 (Fed. Cir. 1983). A definition of "phenylene derivative" that includes one atom is simply too broad to be reasonable. The rejection provides neither evidence nor a persuasive line of reasoning that one of ordinary skill in the art would consider one atom to be a phenylene derivative. A more reasonable interpretation is provided by Merriam-Webster's online Collegiate Dictionary, which defines a derivative as "a chemical substance related *structurally* to another substance and theoretically derivable from it." http://www.m-w.com/cgi-bin/dictionary (emphasis added). One atom simply is not structurally related in any meaningful way to phenylene. Thus, one atom is not a phenylene derivative.

Applicants also respectfully note that claims reciting phenylene derivatives apparently meet the Patent Office's own standards of definiteness, even where the Specification does not further define this term. For example, Claim 6 of U.S. Pat. No. 6,121,378 reads in relevant part:

> 6. The thermosetting powder paint composition according to claim 1, wherein ... Ra, Rb, Rc, Rd and Re represent a ... *phenylene group derivative* ... R^1 and R^2 represent a ... *phenylene group or derivative thereof*, ... R^{16} represents a ... *phenylene group derivative*, R^{26} represents a ... *phenylene group derivative*, ... R^{27} to R^{29} represent a ... *phenylene group derivative* ....

(Emphases supplied). Thus, Claim 43 meets both the Federal Circuit's and the Patent Office's standards for definiteness. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

Claim 43 is further rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. Applicants respectfully traverse.

The rejection states that "[t]he basis for this rejection is that the disclosure of a linker comprising a phenylene is not adequate to describe the full scope of the linkers that are 'derivatives of phenylene.'" Applicants respectfully point out that this is an incorrect standard of written description. The written description requirement applies to the *invention*, and the invention is defined as *whatever is now claimed. See Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991) and references cited therein. There simply is no legal requirement that Applicants describe the full scope of linkers that are derivatives of phenylene because *that is not the claimed invention*. The law is well established that where Applicants claim a composition *comprising* a genus of known compounds, or claim a method of *using or making* a genus of known compounds, the disclosure need only lead one of skill in the art to the genus. For example, in *In re Herschler*, 200 USPQ 711 (C.C.P.A. 1979), the claims at issue recited a method of using steroids generally. The Specification described a method of using dexamethasone 21-phosphate (a steroid) and a method of using an enormously broad genus of compounds[1] that encompassed steroids, but did not specifically mention steroids. Thus, the question before the court was whether description of one broad class of compounds and of one specific compound in that broad class provided adequate written description for a method of using a class of compounds of intermediate scope that was not explicitly mentioned in the disclosure. The court held that it did, holding that:

> [C]laims drawn to the *use* of *known* chemical compounds in a manner auxillary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds.

In re Herschler, 200 USPQ at 718 (emphases in original).

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[1] This broad genus, which the court described as comprising examples that are "awesome in their diversity," *id.* at 717, also included, *inter alia*, antibiotics, barbiturates and rat food. *See id.*

In *In re Robins*, 166 USPQ 552 (C.C.P.A. 1970), Applicants claimed methods of making a genus of urethane polymers. This genus of urethane polymers was disclosed in the Specification. The PTO rejected Applicants' method claims under 35 U.S.C. § 112 because Applicants allegedly did not disclose a sufficient number of species falling within the genus of compounds recited in the method claims. The Court of Customs and Patent Appeals reversed:

> If the examiner and/or the board intended a rejection under the first paragraph of § 112, it must be reversed inasmuch as the specification contains a statement of appellant's invention which is as broad as appellant's broadest claims.
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> * * *
>
> Both the examiner and the board seem to have take the position that in order to "justify," as the examiner said, or to "support," as the board said, broad generic language in a claim, the specification must be equally broad in its naming, and use in examples, of representative compounds encompassed by the claim language. This position, however, misapprehends the proper function of such disclosure. *Mention of representative compounds encompassed by generic claim language clearly is not required by § 112 or any other provision of the statute.* But, where no explicit description of a generic invention is to be found in the specification (which is not the case here) mention of representative compounds may provide an implicit description upon which to base generic claim language.

Id. at page 555 (emphasis supplied). *See also In re Fuetterer*, 138 USPQ 217, 223 (C.C.P.A. 1963) (holding that 35 U.S.C. § 112 was satisfied where a claim recited a composition comprising "an inorganic salt that is capable of holding a mixture of ... carbohydrate and protein in colloidal suspension in water," stating that "Appellant's invention is the *combination* claimed and not the discovery that certain inorganic salts have colloid suspending properties") (emphasis in original). Accordingly, under *Herschler*, *Robbins* and *Fuetterer*, the test for written description of a claimed composition comprising a genus of known compounds is whether the disclosure leads one of skill in the art to the genus *either* by simply disclosing the genus by its name *or* by, for example, disclosing representative compounds encompassed by the genus.

Claim 43 does not recite phenylene derivatives *per se* but rather recites conjugates *comprising* phenylene derivatives. Like the steroids at issue in *Herschler*, phenylene derivatives are well-known in the art. *See, e.g.*, U.S. Pat. Nos. 5,116,853

and 4,994,479. Thus, Applicants need only provide a description of phenylene derivatives that leads one of skill in the art to this class of compounds. They have done this in a straightforward way: by simply stating in the Specification that the conjugates of the invention can comprise a phenylene derivative. *See, e.g.*, the Specification at page 3, lines 15-17. Thus, Applicants have satisfied the legal standard of written description for Claim 43. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

C. Rejection of Claims 4, 15-18, 23-27, 30, 35-37, 42 and 43 under 35 U.S.C. § 102(b)

Claims 4, 15-18, 23-27, 30, 35-37, 42 and 43 are rejected as allegedly anticipated under 35 U.S.C. § 102(b) over U.S. Pat. No. 4,731,439 to Marquardt *et al.* ("the '439 patent"). Claims 23 and 30 are rejected under 35 U.S.C. § 102(b) over Blair *et al.*, 1983, J. Immunological Methods 59:129-43 ("Blair"). Applicants respectfully point out that the rejection is moot with respect to canceled Claim 16 and traverse with respect to the remaining claims.

The standard governing anticipation under 35 U.S.C. § 102 is one of strict identity. The Court of Appeals for the Federal Circuit has held that anticipation can be established only by a single reference that teaches *each and every element* of the claimed invention; anticipation is not shown even if the differences between the claims and the cited reference are argued to be "insubstantial" and the missing elements could be supplied by the knowledge of one skilled in the art. *Structural Rubber Prod. Co. v. Park Rubber Co.*, 221 U.S.P.Q. 1264 (Fed. Cir. 1984). Furthermore, in *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253 (Fed. Cir. 1985) the court pointed out that the assertion of invalidity for lack of novelty is erroneous if a reference teaches "substantially the same thing." A cited reference must meet each claim limitation in order to constitute anticipation.

Neither the '439 patent nor Blair teaches each and every element of any one of the rejected claims. Claims 15 and 23 recite a conjugate comprising, *inter alia*, a native human serum albumin that is not regarded as exogenous by the subject. Each of the rejected claims incorporates this element because each ultimately depends from Claim 15. Neither the '439 patent nor Blair teaches conjugates comprising human

serum albumin. Thus, a *prima facie* case of anticipation has not been advanced. Accordingly, Applicants respectfully request that the instant rejections be withdrawn.

D. Rejection of Claims 4, 5, 15-17, 19, 21, 22, 28, 29, 31-34 and 38-41 under 35 U.S.C. § 103(a)

Each of Claims 4, 5, 15-17, 19, 21, 22, 28, 29, 31-34 and 38-41 is rejected under 35 U.S.C. § 103(a) over one or more combinations of the '439 patent, Blair, U.S. Pat. No. 5,116,944 to Sivam *et al.* ("the '944 patent"), U.S. Pat. No. 5,169,934 to Clark *et al.* ("the '934 patent"), Sezaki *et al.*, 1984, Critical Rev. Therapeutic Drug Carrier Systems 1:1-38 ("Sezaki"), Oseroff *et al.*, 1986, Proc. Natl. Acad. Sci. U.S.A. 83:8744-48 ("Oseroff") and U.S. Pat. No. 4,522,750 to Ades *et al.* ("the '750 patent"). Applicants respectfully point out that the rejections are moot with respect to canceled Claims 16, 19, 28, 29 and 41 traverse with respect to the remaining claims.

A *prima facie* case of obviousness under 35 U.S.C. § 103 satisfies three criteria. First, there must be some suggestion or motivation, either in the cited references or in the art, to modify or combine the cited references. Second, the cited references must provide a reasonable expectation of successfully achieving the claimed invention. That is, they must do more than make the claimed invention merely obvious to try, or obvious to experiment with. *See In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988); *In re Dow Chemical*, 5 USPQ2d 1529 (Fed. Cir. 1988). Nor is it sufficient that one of skill in the art would have been able to produce the claimed invention. *See Orthokinetics v. Safety Travel Chairs*, 1 USPQ2d 1081 (Fed. Cir. 1988). Third, the cited references must teach or suggest each and every element of the claimed invention. *See In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Court of Appeals for the Federal Circuit and the Board of Patent Appeals and Interferences ("the Board") have established exacting standards for determining whether a suggestion or motivation to combine references sufficient to satisfy the first of these requirements exists. As stated by the Board:

> To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan

> would have found the claimed invention to have been obvious in light of the teachings of the references.

Ex parte Clapp, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

Thus, the motivation to combine references must be found in the prior art, not in Applicants' disclosure. *See In re Vaeck*, 20 USPQ2d at 1438.

Furthermore, the cited references must be considered for all that they teach, including portions that teach away from the claimed invention. *See W.L. Gore & Associates*, 220 USPQ at 303. References that teach away from the claimed invention are highly probative of nonobviousness. *See Gillette Co. v. Johnson & Son, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990). It is improper to combine references where the references teach away from their combination. *See id.*; *In re Grasselli*, 218 USPQ 769, 779 (Fed. Cir. 1983).

1. Rejection of Claims 15-17, 19 and 29 over the '439 patent in light of the '944 patent

Claims 15-17, 19 and 29 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over the '439 patent in light of the '944 patent. Applicants respectfully point out the rejection is moot with respect to canceled Claims 16, 19 and 29 and traverse with respect to the remaining claims.

The combination of the '439 patent and the '944 patent fails to make the rejected claims obvious because, *inter alia*, the combination fails to teach or suggest each and every element of the rejected claims. Claim 15 recites conjugates that comprise, *inter alia*, an active substance selected from the group consisting of a chemotherapeutic agent and a photoactive compound. Each of the rejected claims ultimately depends from Claim 15 and so incorporates this limitation. Neither the '439 patent nor the '944 patent teaches or suggests such an active substance, therefore the combination of the '439 patent and the '944 patent fails to teach or suggest each and every element of the rejected claims. Consequently, the combination of the '439 patent and the '944 patent fails to establish a *prima facie* case of obviousness against the rejected claims. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

2. Rejection of Claims 4, 5, 15, 16, 21, 22, 31-34 and 38 over Blair in view of the '944 patent, the '934 patent and Sezaki

Claims 4, 5, 15, 16, 21, 22, 31-34 and 38 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Blair in view of the '944 patent, the '934 patent and Sezaki. Applicants respectfully point out that the rejection is moot with respect to canceled Claim 16 and traverse with respect to the remaining claims.

The cited references fail to establish a *prima facie* case of obviousness because, *inter alia*, there is not a suggestion or motivation in the art to combine the cited references to achieve the claimed invention. The rejection merely recites a list of elements allegedly taught by the cited references and then asserts that the rejected claims are *prima facie* obvious. Thus, the rejection fails to explain where or how the cited references "expressly or impliedly suggest" selecting and combining the listed elements from each of the four cited references in order to produce the claimed invention, or to supply "a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Clapp*, 227 USPQ at 973. Moreover, there is not a motivation to select and combine the particular elements of each reference cited in the rejection because the cited references actually teach away from the claimed invention. The Federal Circuit has held that a reference cited in an obviousness rejection that must be modified in a way that renders it unsatisfactory for its intended purpose teaches away from the claimed invention. *See In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). *See also In re Schulpen*, 157 USPQ 52, 55 (C.C.P.A. 1968) ("[S]uch modification would run counter to [the reference's] teaching by rendering the apparatus inoperative [for its intended purpose]. It seems plain that the [suggestion to modify the reference] must have originated with appellant's own disclosure, and such disclosure, of course, cannot be used against him under 35 U.S.C. § 103.") (citation omitted); MPEP § 2143.01. Blair teaches conjugates comprising *immunoglobulins* for "targeting the agents towards antigens on the surface of cancer cells or T lymphocytes." Blair at page 129. There is no motivation to substitute albumin for immunoglobulin in Blair's conjugates because such a conjugate would not be targeted towards antigens on the surface of cancer cells or T lymphocytes. Furthermore, the

combination of the '944 patent, the '934 patent and Sezaki apparently fails to teach azo-containing linkers, and Blair teaches that the formation of azo-containing linkers has the undesirable side effect of causing extensive precipitation. *See* Blair at page 133. None of the cited references teaches comparable problems using the linkers taught by the '944 or '934 patents. Thus, the cited references teach away from the claimed invention, and there is no suggestion or motivation to combine selected elements of the cited references to achieve the claimed invention. Consequently, a *prima facie* case of obviousness has not been made. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

3. Rejection of Claims 15, 16, 39 and 40 over Oseroff in view of the '944 patent and Blair

Claims 15, 16, 39 and 40 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Oseroff in view of the '944 patent and Blair. Applicants respectfully point out that the rejection is moot with respect to canceled Claim 16 and traverse with respect to the remaining rejected claims.

The cited references fail to establish a *prima facie* case of obviousness because, *inter alia*, the suggested combination renders the references inoperable for their intended purpose, *see Gordon*, 221 USPQ at 1127 and *Schulpen*, 157 USPQ at 55, thus there is not a suggestion or motivation in the art to combine the cited references to achieve the claimed invention. Oseroff teaches a method of killing T-cell leukemia cells using a conjugate comprising chlorin e6 and a monoclonal antibody that targets the conjugate to the leukemic cells. The rejection asserts that it is obvious to replace the monoclonal antibody of the Oseroff conjugate with albumin because "the use of human proteins such as human serum albumin for targeting drugs is known in the art as evidenced by the teachings of Sivam (col. 3, lines 5-29)." Applicants respectfully point out that this is incorrect. The cited portion of Sivam asserts only that "HSA has also been suggested as a targeting agent for *bone imaging agents* comprising *diagnostic* radionucleotides to facilitate delivery of the *diagnostic agent* to soft tissues and blood pool visualization." The '944 patent at column 3, lines 19-22 (emphases added). One of ordinary skill in the art would not be motivated to replace the highly specific leukemic cell targeting monoclonal antibody of the Oseroff

conjugate with human serum albumin. Neither reference explicitly or implicitly suggests this substitution. The '944 patent suggests only that human serum albumin can be used to target a diagnostic agent, not a highly toxic cell killing agent. Furthermore, the '944 patent implies that such a substitution would target Oseroff's lethal conjugate to the subject's soft tissues and blood pool. Neither reference provides a motivation for killing soft tissue or blood cells. Even if one wanted to kill a subject's soft tissue or blood cells, the '944 patent does not teach or suggest that human serum albumin would target the conjugate to these cell types with a specificity sufficient to avoid killing untargeted cell types. Thus, there simply is no motivation to combine Oseroff and the '944 patent. Consequently, the cited references fail to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

4. Rejection of Claims 15 and 41 over Blair in view of the '750 patent

Claims 15 and 41 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Blair in view of the '750 patent. Applicants respectfully point out that the rejection is moot with respect to canceled Claim 41 and traverse with respect to Claim 15.

The cited references fail to establish a *prima facie* case of obviousness because, *inter alia*, they fail to teach each and every element of the claimed invention. Neither Blair nor the '750 patent teaches or suggests a conjugate comprising albumin. Thus, the cited combination of references fails to teach or suggest each and every element of the claimed invention. Consequently, a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

E. Double-Patenting Rejection

Claims 4, 5 and 14-43 are provisionally rejected under 35 U.S.C. § 101 for allegedly being identical to claims in co-pending U.S. Pat. App. Ser. No. 09/641,026. Applicants intend to abandon U.S. Pat. App. Ser. No. 09/641,026, thereby rendering

this rejection moot. Accordingly, Applicants respectfully request that this provisional rejection be withdrawn.

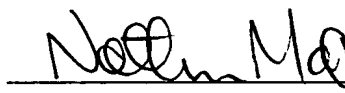
CONCLUSION

In view of the above amendments and remarks, the subject application is believed to be in good and proper order for allowance. Early notification to this effect is earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 493-4935. The commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 16-1150 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: January 31, 2002



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Enclosures